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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/049,887	09/20/2002	Yasunori Chiba	081356-0168	2894

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EXAMINER	
PAK, YONG D	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 09/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/049,887	**Applicant(s)** CHIBA ET AL.	
	Examiner Yong D. Pak	**Art Unit** 1652	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 28 July 2006 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *88 and 92-94*.
   Claim(s) withdrawn from consideration: *89-91 and 95-105*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: see attached.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☐ Other: _____.

ADVISORY ACTION

This application is a 371 of PCT/JP00/05474.

Response to Arguments

The amendment filed on July 28, 2006 under 37 CFR 1.116 in reply to the final rejection has been considered and has been **ENTERED** but is not deemed to place the application in condition for allowance because: the amendments and arguments do not overcome the pending rejections, as discussed below.

Claims 88-105 are pending. Claims 89-91 and 95-105 are withdrawn. Claims 88 and 92-94 are under consideration.

Election/Restrictions

Applicant's argue that Chiba et al. does not disclose the present invention. Examiner respectfully disagrees. The invention of claim 1 comprising a method of preparing a yeast mutant comprising the disruption in its α-1,3-mannosyltransferase (MNN1) gene, mannosylphosphate transferase (MNN4) gene and α-1,6-mannosyltransferase (OCH1) gene, wherein said yeast is used in a method of producing glycoproteins is the common technical feature linking all claims. Chiba et al. discloses such a mutant yeast and a method of making the same. Chiba et al. discloses a "Strategy for genetic manipulation of S. cerevisiae" (description for Figure 1). The definition for "strategy" is "careful plan or method". In Figure 1, Chiba et al. clearly shows a method for making a "genetically manipulated S. cerevisiae" by

disrupting *Δ mnn1Δ mnn4 Δ och1* and introducing α-mannosidase I and (N-acetylglucosaminyl transferase (GnT-I) genes, which are normally found in mammals and not in yeast, into said yeast to produce the yeast-hybrid complex glycoprotein. Therefore, the technical feature linking the above claims does not constitute a special technical feature as defined by PCT Rule 13.2, as it does not define a contribution over the prior art.

Also, claims 89-91 and 95-105 are further drawn to yeast transformed with polynucleotides encoding proteins having different structure and function, which lacks the common technical feature with the method claimed in claims 88 and 92-94 and further requiring different searches in the patent and non-patent literature. Therefore, claims 88-105 do not all share a special technical feature.

The requirement is still deemed proper and is therefore made FINAL.

Claims 89-91 and 95-105 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on April 7, 2005.

Claim Rejections - 35 USC § 112

Claims 88 and 92-94 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as

to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants argue that the claims are fully described because genes encompassed in the claimed method are taught in the prior art and therefore a representative number of species by disclosure of relevant identifying characteristics are disclosed. Examiner respectfully disagrees. A representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. Satisfactory disclosure of a representative number depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. For inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only a few species within the genus. In the instant case the claimed genera of the claims includes species which are widely variant in structure. The claims encompass a method of using any or all yeasts wherein said genes, including any or all recombinants, mutants or variants thereof. The recitation of "α-1,3-mannosyltransferase", "mannosylphosphate transferase", "1,6-mannosyltransferase", "α-mannosidase I" and "N-acetylglucosaminyl transferase-I" fail to provide a sufficient description of the claimed genus of proteins as it merely describes the functional features of the genus without providing any definition of the structural features of the species within the genus. The

CAFC in UC California v. Eli Lilly, (43 USPQ2d 1398) stated that: "in claims to genetic material, however a generic statement such as 'vertebrate insulin cDNA' or 'mammalian insulin cDNA,' without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus." Similarly with the claimed genus of "α-1,3-mannosyltransferase", "mannosylphosphate transferase", "1,6-mannosyltransferase", "α-mannosidase I" and "N-acetylglucosaminyl transferase-I"" proteins, including any or all variants, mutant and recombinants thereof, the functional definition of the genus does not provide any structural information commonly possessed by members of the genus which distinguish the protein species within the genus from other proteins such that one can visualize or recognize the identity of the members of the genus. Therefore, disclosure of solely functional features present in the genus is insufficient to fully describe the whole genus. As discussed in the written description guidelines, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed

correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

Hence the rejection is maintained.

Claims 88 and 92-94 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of preparing a mutant *Saccharomyces cerevisiae* by disrupting MNN1, MNN4 and OCH1 genes normally present in *S. cerevisiae* with selection markers recited in claim 92 and transforming the resulting mutant *S. cerevisiae* with a polynucleotide isolated from *Aspergillus saitoi* and encoding an α-mannosidase I and a polynucleotide isolated from rat and encoding a rat GnT-I, does not reasonably provide enablement for a method of preparing any mutant yeast that produces the glycoprotein of formula (IV) by disrupting any or all MNN1, MNN4 and OCH1 genes and transforming the resulting mutant yeast with a polynucleotide encoding any α-mannosidase I from any source, including recombinants, variants and mutants, and a polynucleotide encoding any GnT-I, including recombinants, variants and mutants. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In response to the previous Office Action, applicants have traversed the above rejection.

Applicants argue that the claims are fully enabled because genes encompassed in the claimed method are taught in the prior art. Examiner respectfully disagrees. The

claims are not limited to any specific genes known in the art, but the method encompasses any or all yeasts wherein any MNN1, MNN4 and OCH1 genes are disrupted and any mannosidase I and GnT genes, including any or all recombinants, mutants or variants thereof, are introduced into said mutant yeast. It would require undue experimentation of the skilled artisan to make and use the claimed variants and mutants of any or all yeast wherein any or all MNN1, MNN4 and OCH1 genes, including any or all recombinants, mutants or variants thereof, are disrupted. As discussed above, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance and predictability of which specific yeast is ideal for the claimed method and which specific α-mannosidase and GnT-I is ideal to transform said mutated yeast and which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. It is this specific guidance that applicants do not provide. Without specific guidance, those skilled in the art will be subjected to undue experimentation of making and testing each of the enormously large number of mutants that results from such experimentation.

Applicants argue that the instant claims are fully enabled because any kinds of α-mannosidase I and any GnT I genes can be used in the present invention and these two genes are only representatives of genes that can be used in the present invention. Examiner respectfully disagrees. The claims are drawn to a method of using any α-mannosidase having any structure and any GnT-I having any structure, including any or

all recombinants, variants or mutants. It would require undue experimentation of the skilled artisan to make and use the claimed variants and mutants of any or all α-mannosidase having and any or all GnT-I, including any or all recombinants, variants or mutants thereof. As discussed above, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance and predictability of which specific yeast is ideal for the claimed method and which specific α-mannosidase and GnT-I is ideal to transform said mutated yeast and which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. It is this specific guidance that applicants do not provide. Without specific guidance, those skilled in the art will be subjected to undue experimentation of making and testing each of the enormously large number of mutants that results from such experimentation.

Hence the rejection is maintained.

Claim Rejections - 35 USC § 102

Claims 88 and 92-94 rejected under 35 U.S.C. 102(b) as being anticipated by Chiba et al.

In response to the previous Office Action, applicants have traversed the above rejection.

Applicants argue that the claims have been amended to recite a "polynucleotide that contains the ORF encoding N-acetylglucosaminyl transferase-I" and Chiba et al. fails to provide a description or suggestion for the "expression of an intact GnT-I reading frame. Examiner respectfully disagrees. Figure 1 describes "Genetically manipulated *S. cerevisiae*", disrupting MNN1, MNN4 and OCH1 genes and introducing various genes to produce new types of sugar chains.

Applicants argue that the present invention is not anticipated by Chiba et al. because the GnT-I gene has not been introduced into host cells but is "an object of our future research" (page 26303". Examiner respectfully disagrees. Although Chiba et al. has not actually introduced a GnT-I gene into the mutant S. cerevisiae in laboratory settings, Chiba et al. discloses a "Strategy for genetic manipulation of S. cerevisiae" (description for Figure 1). The definition for "strategy" is "careful plan or method". In Figure 1, Chiba et al. clearly shows a method for making a "genetically manipulated S. cerevisiae" by disrupting *Δ mnn1Δ mnn4 Δ och1* and introducing α-mannosidase I and GnT-I genes, which are normally found in mammals and not in yeast, into said yeast to produce the yeast-hybrid complex glycoprotein. MPEP 2131 states "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." In the instant application, Figure 1 of Chiba et al. discloses each and every element set forth in the claims, as discussed above. Further, the claims are not drawn to a mutant yeast transformed with GnT-I, but the claims are drawn to a method of making said mutant yeast, which is clearly taught by Chiba. Also, Figure 1 outlining the method of Chiba et

al. is enabling because Chiba et al. teaches yeast wherein *Δ mnn1Δ mnn4 Δ och1* are disrupted and successful expression of both α-mannosidase I and GnT-I in yeast (Pages 26300 and page 26303, last paragraph).

Applicants also argue that Yoshida et al. provides teaches that one having ordinary skill in the art would not expect GnT-I activity *in vitro* is completely maintained *in vivo*, since *in vivo* environment is very complicated compared with *in vitro* environment. Examiner respectfully disagrees. The claims do not recite any limitation of the activity of GnT-I *in vitro* or *in vivo*.

Applicants also argue that in the claimed yeast mutant, a hybrid-tyope sugar chain having formula (IV) is produced, which indicates *in vivo* GnT-I activity in a sugar chain of glycoprotein and Chiba et al. does not describe a mutant yeast capable of producing a hybrid-type sugar chain *in vivo*. Examiner respectfully disagrees. The claims are drawn to a method of making a mutant yeast by disrupting *Δ mnn1Δ mnn4 Δ och1* genes and introducing α-mannosidase I and GnT-I, which Chiba et al. Chiba et al. clearly describes a method of producing the hybrid-type sugar chain of formula (IV) in Figure 1 by introducing a GnT-I gene into a mutant yeast. Production of the hybrid-type sugar would necessarily flow from the mutant yeast of Chiba et al.

Hence the rejection is maintained.

None of the claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong Pak whose telephone number is 571-272-0935.

The examiner can normally be reached 6:30 A.M. to 5:00 P.M. Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

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